Protocol #: 12-0032

**TITLE:** Phase II study of erlotinib for patients with malignant peritoneal mesothelioma (MPeM) exhibiting EGFR mutations.


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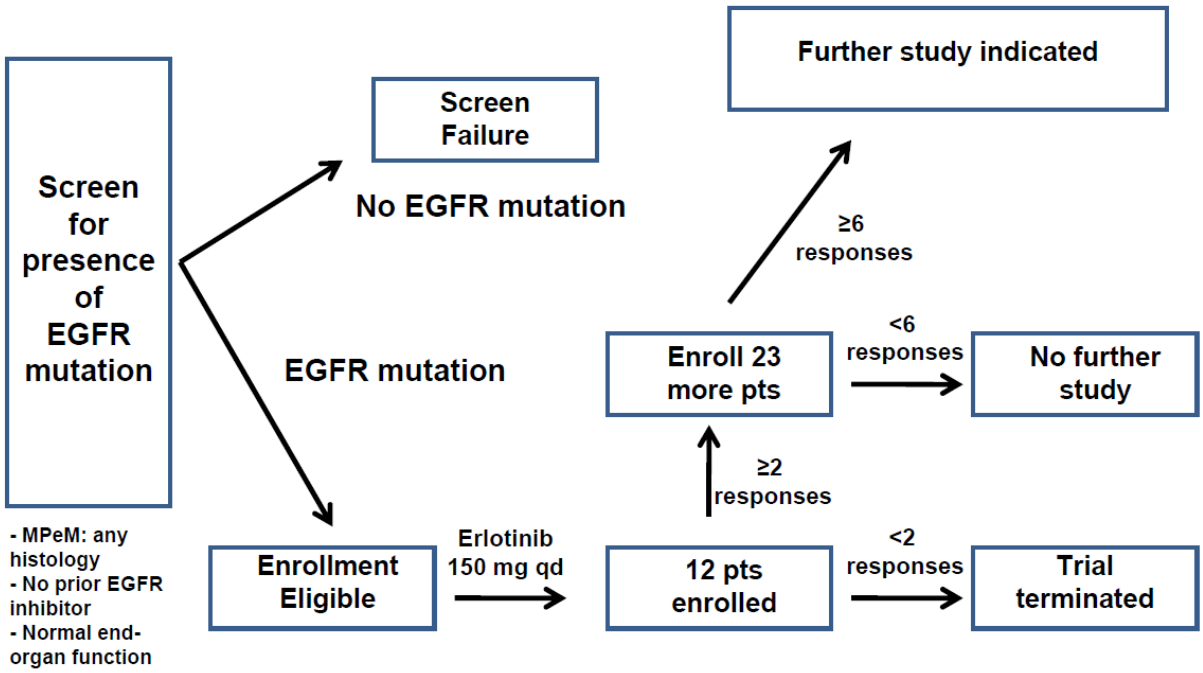
**Astellas Pharmaceuticals Supplied Agent**: Erlotinib (Tarceva)

**Protocol Type / Version # / Version Date:** Original/Version #3 -02/06/2013

**SCHEMA**




**Primary endpoint: Response Rate; Secondary endpoints: PFS, OS, Toxicity**

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**1.2.3.** To determine the disease control rate (CR + PR + SD) of MPeM patients who have EGFR mutations and are treated with erlotinib.

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**1.3.3.** To correlate immunohistochemical staining of EGFR, p-EGFR, MET, E-cadherin, vimentin, and CBL with EGFR mutational status and, if present, particular EGFR mutation noted.

**1.3.4.** To correlate immunohistochemical staining of EGFR, p-EGFR, MET, E-cadherin, vimentin, and CBL with response rate, PFS, and OS in MPeM patients treated with erlotinib.

# 2. BACKGROUND

## 2.1. Malignant Peritoneal Mesothelioma (MPeM)

Malignant mesothelioma is a highly aggressive neoplasm of the serosal lining of the pleura, peritoneum, pericardium, or tunica vaginalis largely attributed to asbestos exposure[1, 2]. It

affects about 2500 to 3000 Americans each year. Malignant peritoneal mesothelioma (MPeM) is the second most common type of mesothelioma and represents approximately 15-20% of all new diagnoses of the disease[2].

Patients with MPeM generally present with non-specific abdominal complaints with pain and/or distention being the most common, though a significant minority of patients can also present with fever, weight loss, or infertility[3]. The most common sign noted in MPeM patients is the development of ascites which can occur in up to 70% of patients and is produced by the multiple tumor nodules present on the peritoneal surface. It is this fluid combined with tumor volume that is the major cause of morbidity in MPeM[3, 4].

Macroscopically, MPeM is characterized by thousands of tumor nodules of variable size and consistency which can coalesce to either form plaques, masses, or layer out evenly to cover the peritoneal surface[4]. Computed tomography (CT) is the current standard to evaluate and characterize the disease and is superior to sonography[5]. While magnetic resonance imaging (MRI) can also be helpful in evaluating patients with MPeM, the longer scan time, increased cost, and difficulty with respiratory motion and bowel peristalsis can interfere with image resolution[3].

While imaging is helpful in the diagnosis of MPeM, as with any malignancy, the definitive diagnosis is made by biopsy. Cytological examination of ascitic fluid rarely results in a positive finding and most patients are instead diagnosed via histology, occasionally after a CT-guided biopsy but, more frequently, with a biopsy performed during laparoscopy or laparotomy[3, 4]. Tumor markers such as serum CA-125 and soluble mesothelin-related peptide (SMRP) can also be measured if findings are suspicious for mesothelioma as many patients with the disease will have increased levels. Though none are sensitive or specific enough to either screen for or to confirm the diagnosis of mesothelioma, respectively, they have each been shown to decrease with treatment and increase with tumor growth and could thus be used to monitor for treatment response[6-8]. CA-125 is a tumor antigen associated with ovarian cancer, but is also elevated in patients with MPeM[6] while SMRP is a cell surface protein highly expressed in mesothelioma attached to the cell surface[2, 7].

The histopathological diagnosis of MPeM requires a series of immunohistochemical studies to distinguish it from adenocarcinoma. Calretinin, cytokeratins 5/6, WT-1, thrombomodulin, and mesothelin are usually positive while B72.3, CEA, CD 15, Leu-M1, and BER-EP4 immunostains are generally negative[3]. There are a variety of histological subtype classifications though these can be grouped broadly into epithelial, sarcomatoid, or a combination of the two known as biphasic disease. More than 75% of patients with MPeM have purely epithelial disease with 10-15% having a pure sarcomatoid histology[3]. Prognostically, patients with the epithelial subtype fare significantly better than their sarcomatoid or biphasic counterparts as is also seen with malignant pleural mesothelioma (MPM)[2, 4, 9].

Treatment for MPeM has traditionally relied upon cytoreductive surgery with chemotherapy delivered intraperitoneally and/or systemically[10]. Cytoreductive surgery is the mainstay of this treatment as most patients will eventually die from obstruction due to tumor compression[3, 4].

Surgery allows for a maximal debulkment of resectable tumor and the lysis of adhesions between bowel loops. While rarely curative, this procedure minimizes tumor volume and future complications when the tumor begins to grow again. Cytoreduction also allows for the more effective delivery of intraperitoneal chemotherapy[3]. While a variety of regimens have been used, the chemotherapy used is generally heated as hyperthermia can have direct cytotoxic effects and there is greater depth of penetration of the chemotherapy agents into the tumors[3, 4, 9]. Cytoreductive surgery followed by intraperitoneal chemotherapy has been associated with a median survival of 34-92 months and 5-year survival rates reported at 33-59%[9, 11, 12]. Once a patient is deemed to no longer be a surgical candidate, treatment often relies on systemic chemotherapy alone. As with pleural mesothelioma, the most common regimen used is a combination of a platinum with pemetrexed[13-15] though pemetrexed combined with gemcitabine has also been reported[15]. The median survival reported for previously treated patients with a platinum/pemetrexed combination was 13 months[13] while the median survival for the patients treated with first-line gemcitabine/pemetrexed was 26.8 months[15]. Once patients fail these regimens there are no standard therapeutic options.

Prognostically, in MPeM, women fare significantly better than men. This is likely multifactorial and could relate to the higher rates of epithelial disease in women compared to men[3, 16]. However, an interesting distinction between the sexes is that men are much more likely to have an asbestos exposure history, and it has been postulated that it is the underlying cause of the disease which is the true prognostic factor. In men, MPeM often has an aggressive disease course with a median survival of less than one year while women have a far more indolent disease with a median survival that ranges from 3 to 5 years[16].

While EGFR inhibition has been attempted in the treatment of pleural mesothelioma, there have been no significant clinical responses despite almost-universal over-expression of EGFR via immunohistochemistry in this disease[17, 18]. This is felt to be secondary to the fact that EGFR mutations – a predictor of response in the first-line treatment of patients with non-small cell lung cancer (NSCLC) – appear to be non-existent in pleural mesothelioma[19]. Recently reported data by Foster and colleagues suggests that MPeM, however, exhibits an increased rate of EGFR mutations – both previously undescribed mutations as well as the known L858R activating mutation – as high as 31%[20], and it appears that these are activating mutations with sensitivity to EGFR TKIs[21]. This is far in excess of that seen in pleural mesothelioma and compares favorably with the rate seen in NSCLC in which such mutations have been reported in just 7-22% of Western-population patients, though noted in up to 50% of Asian patient populations[22-24].

## 2.2. Erlotinib

Erlotinib (Tarceva, Astellas) is an orally active, potent, selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. Erlotinib was initially approved in November 2004 by the United States Food and Drug Administration (FDA), and in September 2005 by the European Agency for the Evaluation of Medicinal Products (EMEA) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least 1 prior chemotherapy regimen. Erlotinib has since been FDA- approved for maintenance therapy in NSCLC and for first-line treatment of pancreatic cancer when

combined with gemcitabine. NCCN guidelines now recommend erlotinib for first-line treatment of NSCLC in those patients who exhibit a mutation in the epidermal growth factor receptor.

### 2.2.1. Summary of Erlotinib Safety

The safety of single-agent erlotinib has been evaluated in healthy volunteers and/or cancer patients at doses ranging from 1 mg to 1600 mg and for durations greater than 24 months. There have been 10 single-agent studies completed in cancer patients and 10 single-agent studies completed in healthy volunteers. The most relevant data for safety evaluation of single-agent erlotinib have been collected in the large randomized, double-blind, phase 3 study of erlotinib 150 mg/day compared with placebo conducted in patients who failed at least 1 prior chemotherapy regimen for advanced/metastatic NSCLC (BR.21)[25]. This phase 3, placebo-controlled study is the primary basis for evaluating the safety of single-agent erlotinib.

The most frequent adverse events (AEs) observed in clinical trials and consistent among EGFR inhibitors are the development of dermatological manifestations including a rash, erythema, and dry skin, as well as diarrhea[25, 26]. Other less frequent events include mild to moderate nausea, vomiting, anorexia, and asthenia. The incidence of rash ranges from 75%-85% of patients while diarrhea has been reported in over half of the erlotinib-treated patients in the BR.21 trial. Grade 3 or 4 adverse events were reported in 62% of patients in the erlotinib arm and 58% of patients in the placebo arm in Study BR.21. Grade 3 or 4 events in Study BR.21 were events that are frequently associated with NSCLC; dyspnea and fatigue occurred at a similar rate in the 2 treatment arms. Treatment-related grade 3 or 4 events occurred in 5% of patients who received placebo and 23% of erlotinib-treated patients (primarily grade 3 rash and diarrhea)[25].

Less common AEs for which the incidence in the BR.21 erlotinib arm was at least twice the incidence in the placebo arm include stomatitis (17% vs 3%), conjunctivitis (12% vs 2%), keratoconjunctivitis sicca (12% vs 3%), and epistaxis (7% vs < 1%). Overall, data from clinical studies confirm that erlotinib is not associated with any significant myelotoxicity, even in patients with extensive prior chemotherapy. Liver function abnormalities, including elevated serum ALT, AST, and/or bilirubin, have been observed infrequently in the treatment of NSCLC with single-agent erlotinib at 150 mg/day. Dose reductions or discontinuation due to AEs occurred in 19% and 7% of erlotinib-treated patients, respectively[25].

As with other drugs in this class of agents, interstitial lung disease (ILD)-like events have been observed (see **Section 7.8**). There have been infrequent reports of serious ILD-like events (including fatalities) in patients receiving erlotinib for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In the single-agent study in patients with NSCLC, Study BR.21, the incidence of ILD-like events (0.8%) was the same in the placebo and erlotinib groups. In the combination study with gemcitabine in patients with pancreatic cancer, study PA.3, the incidence of ILD-like events was 2.5% versus 0.4% in the erlotinib plus gemcitabine versus the placebo plus gemcitabine groups, respectively. The overall incidence in erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.7% out of approximately 4900 patients. No imbalance was

noted in the incidence of ILD-like events between treatment groups in the single-agent, randomized, placebo-controlled Study BR.21, or in the 2 large first-line NSCLC studies (Study OSI2298g, Study BO16411), which utilized a standard platinum-based regimen with or without erlotinib. Since this was not the case when erlotinib was used concurrently with gemcitabine in the placebo-controlled study PA.3, a potential causal relationship between erlotinib exposure and the rare occurrence of ILD cannot be completely ruled out. For more information, refer to the erlotinib Investigator's Brochure.

### 2.2.2. Summary of Erlotinib Efficacy

Phase 2 studies of single-agent erlotinib in the treatment of advanced solid tumors indicated antitumor activity in NSCLC, head and neck, and ovarian cancers. Study BR.21 was a multi-center, randomized, double-blind, placebo-controlled, phase 3 study of single-agent erlotinib 150 mg/day in patients with NSCLC. In this study, 731 patients with stage IIIB/IV NSCLC, after failure of at least 1 prior chemotherapy regimen, were randomized (2:1) to receive daily erlotinib or placebo. Statistically significant and clinically relevant prolongation in OS was observed for erlotinib compared with placebo (median 6.7 vs 4.7 months; HR 0.73; 95% CI, 0.61 – 0.86, $P < 0.001$), indicating that erlotinib reduced the risk of death by 27% compared with placebo[25].

Secondary endpoints of progression-free survival (PFS) and response rate were also significantly greater for erlotinib. The planned quality of life analysis, time to deterioration of patient-reported symptoms, showed statistically significant and clinically meaningful benefit for patients randomized to erlotinib[25].

In pleural mesothelioma, despite over-expression of EGFR via immunohistochemistry, EGFR inhibition resulted in no significant clinical responses[17, 18]. As noted earlier, EGFR mutations in pleural mesothelioma appear to be non-existent[19]. This lack of correlation between EGFR over-expression and response to EGFR-targeted therapy[27, 28] is an important observation that has since evolved into the realization that the most important factor allowing for response when exposed to EGFR inhibition is the presence of activating mutations in the EGFR tyrosine kinase domain[29, 30].

**Rationale**

In pleural mesothelioma (MPM), EGFR is highly over-expressed in most cell lines and tumors[31]. Although the EGFR tyrosine kinase inhibitor gefitinib inhibits mesothelioma *in vitro*, phase II trials of gefitinib and erlotinib in MPM by the Cancer and Leukemia Group B and the Southwest Oncology Group, respectively, reported no activity[17, 18]. Despite EGFR over-expression via immunohistochemistry (IHC) in >90% of MPM patients, EGFR activating mutations have been rarely observed and the largest published series evaluating for such mutations detected none[19]. There is significant as a lack of correlation between EGFR over-expression and response to EGFR-targeted therapy has also been observed in non-small-cell lung cancer (NSCLC)[27, 28] while activating mutations in the EGFR tyrosine kinase domain have instead been associated with clinically significant responses when targeted by an EGFR TKI[29, 30].

Data from Foster and colleagues revealed that MPeM exhibits an increased rate of EGFR mutations – both previously undescribed mutations as well as known activating mutations such as the L858R mutation[20]. Up to 31% of MPeM tumor samples exhibited these mutations and it appears that these are activating mutations with sensitivity to EGFR TKIs[20, 21]. Erlotinib, an oral EGFR TKI, is currently FDA-approved for NSCLC but to-date has never been formerly investigated as treatment for MPeM[32].

It is noteworthy that of the EGFR mutations in MPeM, most have never been previously reported. While well-described exon 19 deletions or L858R point mutations in exon 21 have shown increased response rates in patients with NSCLC who are treated with EGFR TKI's, other mutations – in particular the secondary T790M mutation – in addition to MET amplification have demonstrated resistance to treatment with the same agents[33, 34]. While some preliminary data shows that the EGFR mutations in MPeM are indeed activating mutations, this information is based on a small sample and it is not fully known how these and other potentially discoverable EGFR mutations will respond to erlotinib[21]. As such, the different EGFR mutations noted in MPeM in this trial will be correlated with response to erlotinib in the final outcome analysis.

## 3. PATIENT SELECTION

### 3.1. Eligibility Criteria

**3.1.1.** Histologically- or cytologically-confirmed malignant peritoneal mesothelioma (MPeM); epithelial, sarcomatoid, biphasic, multi-cystic, or well-differentiated papillary subtypes are allowed.

**3.1.2.** A tumor block or 10 unstained slides must be available for determining EGFR mutational status. Only those patients who have a mutation of the EGFR tyrosine kinase domain will be able to enroll in this study.

**3.1.3.** Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques or as $\geq$10 mm with spiral CT scan. See Section 10 for the evaluation of measurable disease.

**3.1.4.** No prior use of EGFR tyrosine kinase inhibitors or monoclonal antibodies; all other prior treatments are allowed if $\geq$ 4 weeks since treatment completed, including chemotherapy (systemic or intraperitoneal), radiation therapy, and/or surgery. There is no limit on the number of previous treatments allowed.

**3.1.5.** Age $\geq$18 years. Because no dosing or adverse event data are currently available on the use of erlotinib in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric single-agent trials, if applicable.

**3.1.6.** Life expectancy of greater than 3 months.

**3.1.7.** Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (see Appendix A).

**3.1.8.** Patients must have normal organ and marrow function as defined by the following required laboratory values obtained ≤ 14 days before enrollment:

| | |
|---|---|
| leukocytes | ≥2,000/mcL |
| absolute neutrophil count | ≥1,500/mcL |
| platelets | ≥100,000/mcL |
| total bilirubin | ≤ 1.5 X institutional ULN |
| AST(SGOT)/ALT(SGPT) | ≤2.5 X institutional ULN |
| creatinine | ≤ 2 X institutional ULN |
| | OR |
| creatinine clearance | ≥30 mL/min/1.73 $m^2$ for patients with creatinine levels above institutional normal |

**3.1.9.** The effects of erlotinib on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

**3.1.10.** Ability to understand and the willingness to sign a written informed screening and treatment consent.

**3.2.** Exclusion Criteria

**3.2.1.** Chemotherapy, radiotherapy, or surgery within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

**3.2.2.** Patients may not be receiving any other investigational agents.

**3.2.3.** Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

**3.2.4.** History of allergic reactions attributed to compounds of similar chemical or biologic composition to erlotinib.

**3.2.5.** EGFR-mutation negative tumor tissue as determined by sequencing. If an individual tissue test result is inconclusive (unable to be determined), it will be considered negative for study eligibility purposes.

**3.2.6.** History of previous malignancy excluding non-melanoma skin lesions and in-situ cervical cancer. Patients with other malignancies are eligible if they have been disease free for ≥ 3 years.

**3.2.7.** Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

**3.2.8.** Pregnant women are excluded from this study because it is unknown if erlotinib poses a potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with erlotinib, breastfeeding should be discontinued if the mother is treated with erlotinib.

**3.2.9.** HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with erlotinib. In addition, these patients are at increased risk of lethal infections. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

**3.2.10.** Inability to tolerate or absorb an oral medication due to any cause, including but not limited to malabsorption syndromes.

### 3.3. Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

## 4. REGISTRATION PROCEDURES

### 4.1. General Guidelines

Eligible patients will be entered on study centrally at the University of Chicago by the Study Registrar, **Peter Ostiguy** at **773-834-1472** or **postiguy@medicine.bsd.uchicago.edu.**

Following registration, patients should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Registrar should be notified of cancellations as soon as possible.

### 4.2. Registration Process

All patients must be registered with the University of Chicago Registrar, **Peter Ostiguy** at least

48 hours prior to the commencement of treatment. The following documents should be completed by the research nurse and emailed **postiguy@medicine.bsd.uchicago.edu** or faxed **773-834-1798** to the Registrar:

- Provider of information
- Treating Physician
- Patient name and hospital ID number
- Patient's zip code of residence
- Date & copy of signed screening and treatment informed consents
- Race, gender, date of birth of patient
- Diagnosis and date of initial diagnosis
- EGFR mutational analysis results
- Source documentation for eligibility and pre-study procedures

The research nurse or data manager will then call **773-834-1798** or e-mail **postiguy@medicine.bsd.uchicago.edu** to confirm all selection criteria listed in Section 4.0. To complete the registration process, the Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Call the research nurse or data manager and verbally confirm registration

## 5. TREATMENT PLAN

A separate screening consent must be signed for the screening process for any patient to have his/her tissue evaluated for EGFR mutational status. If the patient's tumor exhibits an EGFR mutation, the patient will then be offered a separate treatment consent for enrollment in clinical trial allowing for the administration of erlotinib.

### 5.1. Erlotinib Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for erlotinib are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

#### 5.1.1. Formulation

Astellas will supply tablets containing erlotinib hydrochloride equivalent to 150 mg, 100 mg, and 25 mg of erlotinib. All tablets are round, white, film-coated, and bi-convex with no imprint. Additional information can be found in the erlotinib Investigator's Brochure.

#### 5.1.2. Packaging and Labeling

Study drug tablets will be supplied in blue-white, high-density, polyethylene bottles of 30 tablets each. The bottles will have a tamper-evident seal and a child-resistant cap. Each bottle will have a unique identifier (bottle number).

### 5.1.3. Storage and Handling

Study drug tablets should be stored between 15°C and 30°C (59°F and 86°F).

### 5.1.4. Administration

Study drug therapy must start within 14 days of registration. The date the patient takes the first dose of study drug will be considered Day 1 of this study. Study drug tablets should be taken at approximately the same time each day, preferably in the morning.

Each study drug dose is to be taken with up to 200 mL (~ 1 cup or 8 oz) of water, and should be taken either 1 hour before or 2 hours after a meal or medications, including vitamins and other supplements. The starting dose of erlotinib is 150 mg daily (see **Table 6-1**). Consumption of grapefruit and grapefruit juice should be avoided while on study drug therapy (see **Section 5.4.3**).

The entire dose must be taken at one time. If the patient vomits after taking the tablet(s), the dose should be replaced only if the tablet(s) can actually be seen and counted.

## 5.2. Drug Accountability

Astellas requires that a drug accountability log be maintained. The information contained on the log should be sufficient to comply with applicable GCP regulations. Drug accountability log information may include, but is not limited to, the following: number of bottles and date the study drug was received, number of bottles dispensed to each patient (including bottle number, date dispensed/returned, patient identifier information, protocol number, dose, and lot/batch number) quantity of tablets returned by the patient, current balance, and the initials of the person who recorded the accountability log information.

## 5.3. Treatment Compliance

Compliance will be assessed by counting tablets at the scheduled patient visits. Data regarding missed or modified doses will be recorded in the case report form (CRF).

## 5.4. General Concomitant Medications and Supportive Care Guidelines

All concomitant medications will be recorded in patient record through Post-treatment.

### 5.4.1. Permitted Concomitant Medications

#### 5.4.1.1 Anti-rash and Anti-diarrheal Therapies

Skin rash or dermatosis has been observed in many patients during treatment with erlotinib. There have been no clinical trials formally evaluating treatments for rash induced by erlotinib.

Patients who develop a mild rash characterized by pustules or raised, red areas may be treated with topical therapy such as corticosteroids or topical clindamycin. Oral tetracycline or oral minocycline may be used at the discretion of the investigator if more severe. (NOTE: minocycline is known to interfere with anticoagulants and oral contraceptives. Patients treated with minocycline who are taking anticoagulants and/or oral contraceptives should be monitored accordingly). Retinoids and other acne medications such as benzoyl peroxide are not recommended, given that the pathology of the rash is not related to acne pathology and that these agents are more likely to exacerbate the rash due to their drying effects on the skin.

Guidance concerning modification of study drug dosing is provided in **Table 6-2** while guidance concerning the treatment of rash is provided in **Table 6-3.**
Anti-diarrheal medications may be introduced if symptoms occur. Previous trials have shown that the frequency and severity of diarrhea rarely hindered the administration of erlotinib and that the diarrhea could be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea-free for 12 hours.

#### 5.4.1.2 Anticoagulant Therapies

Concomitant treatment with warfarin or a coumadin-derived anticoagulant is permitted provided increased vigilance occurs with respect to monitoring international normalized ratio (INR). INR elevations and/or bleeding events have been reported in some cancer patients taking warfarin while on erlotinib. For this study, patients taking warfarin or other coumadin-derived anticoagulants while on study drug should be monitored as clinically indicated for changes in INR, especially when the study drug is being started or stopped.

### 5.4.2. Prohibited Concomitant Medications

#### 5.4.2.1 Cytotoxic or Hormonal Therapy and Biological or Immune Response Modifiers

No other cytotoxic therapy, EGFR inhibitor therapy, hormonal therapy, or biological or immune response modifiers for the treatment of cancer may be administered to patients while they are on study drug.

#### 5.4.2.2 Radiotherapy

The need for radiotherapy will be considered indicative of disease relapse, and these patients will be discontinued from study drug and will enter the Post-treatment period of the study.

#### 5.4.2.3 Other Investigational Drug Therapies

Patients should not receive any other investigational drugs during the On-treatment period of the study.

### 5.4.3. Potential for Drug Interactions

Erlotinib is protein bound (92% to 95% in humans) and metabolized by hepatic CYP3A4 and CYP1A2 and pulmonary CYP1A1 enzymes. Therefore, a potential for drug-drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound or that are CYP3A4 or CYP1A inhibitors/inducers (**Appendix B**).

Substances that are potent inhibitors of CYP3A4 activity (eg, ketoconazole) decrease erlotinib metabolism and increase erlotinib plasma concentrations. This increase may be clinically relevant as adverse experiences are related to dose and exposure. Therefore, caution should be used when administering CYP3A4 inhibitors to patients who are on study drug. Grapefruit and grapefruit juice contain a strong inhibitor of CYP3A4 that may increase exposure to erlotinib. Therefore, patients in this study should avoid consuming grapefruit and grapefruit juice while on study drug therapy.

Pre-treatment with the CYP3A4 inducer rifampicin decreases erlotinib AUC by about two-thirds. Alternate treatments lacking CYP3A4 inducing activity should be considered. If still smoking, patients should also be advised to quit due to the induction effect of tobacco on the CYP1A2 enzyme. For more information, refer to the erlotinib Investigator's Brochure.

As mentioned in **Section 5.4.1.2**, INR elevations and/or bleeding events have been reported in some cancer patients taking warfarin while on erlotinib. For this study, patients taking warfarin or other coumadin-derived anticoagulants while on study drug therapy should be monitored as clinically indicated for changes in INR, especially when the study drug is being started or stopped.

### 5.4.4. Ophthalmologic Considerations

Patients with dry eyes should be advised to use an ocular lubricant. Patients who continue to wear contact lenses may have an increased risk of ocular AEs (eg, keratitis). Patients may continue to wear contacts but should discuss this issue with their treating oncologist before going on study. In addition, any elective ophthalmological surgery while the patient is taking study drug must first be discussed between the investigator.

### 5.4.5. Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

### 5.5. Duration of Follow-up

Patients will be followed until progression or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse events

### 5.6. Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

### 6.1. Dose Modifications

The dose of study drug **will not** be escalated above 150 mg/day for any reason. Doses of study drug may be reduced and/or delayed for toxicities at any time during the study. If a patient experiences several toxicities, dose modifications are to be made according to the body system showing the greatest degree of toxicity. Toxicities will be graded by using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Refer to the following website for the CTCAE manual or the CTCAE document:

**http://ctep.cancer.gov/reporting/ctc.html**

#### 6.1.1. Dose Reduction and Re-escalation

In the event of a toxicity that is not tolerated due to symptoms, disfigurement or interference with normal daily activities (regardless of severity), or is not controlled by optimal supportive care, the daily dose of study drug will be decreased according to the schedule below (**Table 6-1**). If significant toxicity is still apparent, the dose may be reduced a second time.

Patients who require a dose reduction must be evaluated at least monthly until the toxicity stabilizes or improves. Once determined to be stable, patients can resume evaluations according to the protocol-specified visit schedule. The following applies to dose reductions and re-escalations:

Doses that have been reduced to 100 mg/day may be re-escalated to 150 mg/day, but only if the toxicity that led to the dose reduction has abated or returned to baseline severity, and the investigator believes it is in the best interest of the patient.

Doses that have been reduced to 50 mg/day may be re-escalated to 100 mg/day, but only if the toxicity that led to the dose reduction has abated or returned to baseline severity, and the investigator believes it is in the best interest of the patient. **Doses that have been reduced to 50 mg/day may never be re-escalated to a dose higher than 100 mg/day.**

**If any dose is re-escalated, patient must be seen by investigator in 14 days to assess toxicity.** Patients whose dose is re-escalated must be then evaluated at least monthly to assess for toxicity. Once determined to be stable, patients can resume evaluations according to the protocol-specified visit schedule. Any patient who fails to tolerate treatment with 50 mg/day will be discontinued from study drug and enter the Post-treatment period of the study. Recommendations for dose modification are outlined in **Table 6-2**.

**Table 6-1: Dose reduction levels**

| Dose Level | Erlotinib Dose |
|---|---|
| 0 | 150 mg/day |
| -1 | 100 mg/day |
| -2 | 50 mg/day |

**Table 6-2: Dose modification guidelines**

| Toxicity – CTCAE v 4.0 | Dose Modification[a] |
|---|---|
| **Diarrhea** | |
| Grade 1 or 2 | None. Initiate therapy with loperamide. |
| Grade 3[b] or 4[b] | Interrupt study drug until resolution to ≤ grade 2 and then restart 1 dose level lower. |
| **Rash** | |
| Grade 1 | None. |
| Grade 2 | None. If rash persists or worsens over 14 days despite treatment as outlined in **table 6-3**, then reduce by 1 dose level. |
| Grade 3[b] | Reduce by 1 dose level. If rash persists or worsens over 10-14 days, then interrupt study drug until resolution to ≤ grade 2 and then restart 1 dose level lower. |
| Grade 4 | Permanently discontinue study drug. |
| **Interstitial Lung Disease** | |
| Any Grade | If ILD is suspected, study drug should be interrupted immediately pending diagnostic evaluation. If ILD is diagnosed, study drug should be discontinued permanently. |
| **Other Treatment-related Toxicities** | |
| Grade 1 or 2 | None. |
| Grade 3[b,c] | Interrupt study drug until resolution to ≤ grade 2 and then |

| | |
|---|---|
| | restart 1 dose level lower. |
| Grade 4 | Permanently discontinue study drug. |
| A Doses that have been to reduced to 100 mg/day may be re-escalated to 150 mg/day, but only if the toxicity that led to the dose reduction has abated or returned to baseline severity, and the investigator believes it is in the best interest of the patient. Doses that have been reduced to 50 mg/day may be re-escalated to 100 mg/day, but only if the toxicity that led to the dose reduction has abated or returned to baseline severity, and the investigator believes it is in the best interest of the patient. Doses that have been reduced to 50 mg/day may never be re-escalated to a dose higher than 100 mg/day. Any patient who fails to tolerate treatment with 50 mg/day will be discontinued from study drug and enter the post-treatment period of the study.<br><br>B If the event does not resolve to ≤ grade 2 by ≤ 21 days, study drug will be discontinued.<br><br>C Only if ≥ 2 grade level change from baseline. | |

**Table 6-3: Rash treatment guidelines.**

| Rash Grade | Recommended Treatment |
|---|---|
| Grade 1 | No treatment or topical hydrocortisone 1% cream and/or clindamycin 1% gel at investigator's discretion |
| Grade 2 | Hydrocortisone 2.5% cream or clindamycin 1% gel PLUS doxycycline 100 mg po bid or minocycline 100 mg po bid[a] |
| Grade 3 | Hydrocortisone 2.5% cream or clindamycin 1% gel PLUS doxycycline 100 mg po bid or minocycline 100 mg po bid[a] PLUS methyprednisolone dose pack |
| Grade 4 | Per Institutional Guidelines. |
| A Minocycline is known to interfere with anticoagulants and oral contraceptives. Patients treated with minocycline who are taking anticoagulants and/or oral contraceptives should be monitored accordingly.<br>Note: Retinoids and other acne medications such as benzoyl peroxide are not recommende given that the pathology of the rash is not related to acne pathology and that these agents a more likely to exacerbate the rash due to their drying effects on the skin. | |

### 6.1.2. Dose Interruption

Patients who have a continuous interruption of dosing for ≤ 21 days in a row may have study drug re-started at the appropriate dose, provided any toxicities have improved as outlined above.

Patients who have a continuous interruption of dosing for > 21 days in a row generally should not be allowed to re-start study drug therapy and should enter the Post-treatment period of the study. However, re-starting study drug after > 21 days of dose interruption may occur provided any toxicities have improved as outlined above **AND** the investigator believes it is in the best interest of the patient.

## 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (**Section 7.1**) and the characteristics of an observed AE (**Section 7.2**) will determine whether the event requires expedited reporting **in addition** to routine reporting.

## 7.1. Definition of Adverse Drug Reaction

An adverse drug reaction (ADR) is any response to a medicinal product that is noxious and/or unintended and related to any dose. The phrase, "response to a medicinal product", means that a causal relationship between the medicinal product and the AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

## 7.2. Definition of Adverse Event

An **Adverse Event** or adverse experience is any untoward medical occurrence in a patient or clinical investigation patient administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions, which increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials, will also be considered as adverse experiences. Adverse events may also include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (eg, invasive procedures such as biopsies).

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the first date of study drug administration should be considered as pre-existing and should be documented as baseline signs and symptoms in the CRF.

An AE **does not** include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the AE;
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions);
- Overdose of either study drug or concomitant medication without any signs or symptoms unless the patient is hospitalized for observation.

## 7.3. Evaluating and Reporting of Adverse Events

All AEs (ie, a new event or an exacerbation of a pre-existing condition) that occur in the course of the clinical study (ie, from the time of randomization until 30 days from the last dose of study drug) must be recorded as an AE or SAE on the appropriate page(s) of the CRF and SAE form, as applicable. All study drug-related SAEs occurring more than 30 days after the last dose of study drug must also be reported. The evaluation of an AE should continue until the AE resolves, or until the investigator and/or sponsor determine the

patient's condition is stable. All patients who have received at least 1 exposure to study therapy will be evaluated for safety of study treatment.

### 7.4. Assessment of Adverse Events

All AEs will be assessed by the investigator and recorded on the appropriate case report form (CRF), including the dates of onset and resolution, severity, relationship to study drug, seriousness, and whether the event caused the patient to withdraw from the study.

**Severity:** Severity should be recorded and graded according to the NCI CTCAE, v4.0 (refer to the following website for the CTC manual or the CTC document):

**http://ctep.cancer.gov/reporting/ctc.html**

**Relationship:** The relationship to study drug should be assessed using the following definitions:
**Not Related:** Evidence exists that the AE has an etiology other than the study drug (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication);
**Related:** A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the patient's clinical state, intercurrent illness or concomitant therapies. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is not considered related to study drug, then an alternative explanation should be provided.

### 7.5. Serious Adverse Events

An SAE is defined as follows:
Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- Life-threatening situation (patient is at immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy, disease-related procedures, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events);
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a patient who received study drug;
- Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm;
- Blood dyscrasias or convulsions that do not result in hospitalization;
- Development of drug dependency or drug abuse.

**Clarification of SAEs**

- Death is an outcome of an AE and not an AE in itself. In reports of death due to "Disease Progression", where no other information is provided, the death will be assumed to have resulted from relapse of the disease being treated with the study drug(s);

- All SAEs, regardless of cause, must be reported for patients on study (≤ 30 days from last study drug dose);

- All SAEs occurring more than 30 days after last study drug administration and considered at least possibly drug-related must also be reported;

- "Occurring at any dose" does not imply that the patient is receiving study drug at the time of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE but may have contributed to the event; event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity;

- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE;

- "Inpatient hospitalization" means the patient has been formally admitted to a hospital for medical reasons, for any length of time. Presentation and care within an emergency department does not necessarily constitute an SAE;

- The investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.
-

## 7.6. Serious and Unexpected Suspected Adverse Reaction (SUSAR)

A serious adverse event is considered to be a suspected adverse reaction if there evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon is the study population, or an aggregate analysis of specific events occurring at greater frequency than expected from historical controls.

Unexpected events are those not listed at the observed specificity or severity in the protocol, consent, investigator brochure, FDA-approved package insert, or elsewhere in the current IND application. This includes adverse events listed in the protocol, consent or IND as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but

which have not been previously observed with this investigational agent.

**ALL SUSARS occurring on this clinical trial must be reported to the FDA. Refer to Section 7.7 for reporting guidelines.**

## 7.7. Serious Adverse Event Reporting Requirements

### 7.7.1. University of Chicago Reporting Guidelines

All serious adverse events and protocol deviations must also be reported to the University of Chicago Comprehensive Cancer Center (UCCCC) Cancer Clinical Trials Office (CCTO). Relevant events will be reported to the University of Chicago Institutional Review Board (UCIRB) in accordance with their current policies. The Research Nurse or other designated individual should report the SAE/deviation to the UCCCC Quality Assurance (QA) Operations Manager by the end of the business day when s/he becomes aware of the event. Events occurring after business hours will be reported to the CCTO by 12pm (noon) the next business day. Events may be reported to the UCCCC QA Manager by phone at (773)-702-5149 or email (qaccto@bsd.uchicago.edu).

The following information is required when reporting the event to the CCTO:

- Reporter's Name and Telephone Number
- Patient Initials
- Patient Medical Record Number
- IRB Protocol Number
- Name of study principal investigator
- Attending Physician
- Date of Event
- Description of event (include grade of the event and if the event required hospitalization.)
- Whether or not the event meets the IRB's reporting criteria

When appropriate, the IRB's Unanticipated Problems electronic submission form must be completed by the research nurse or other designated individual and submitted by the investigatorvia the IRB's electronic submission system within **the IRB's designated reporting timeframes**.

Details of the IRB's current policy can be found on their website at:
http://bsdirb.bsd.uchicago.edu/forms-guidelines/up.html

### 7.7.2. Astellas Pharmaceuticals Reporting Guidelines

OSI has requirements for expedited reporting of SAEs to worldwide regulatory authorities; therefore, the appropriate parties must be notified immediately regarding the occurrence of any SAE that occurs after the patient has registered for the On-treatment portion of the study.

The procedures for reporting SAEs, regardless of causal relationship, are as follows:

- Complete the Serious Adverse Event Report Form;
- Details of the actual SAE routing in each specific country/region will be provided as part of the study procedures manual;
- Serious Adverse Event Report Form must be faxed ≤ 24 hours of the investigator's knowledge of the event using the following fax numbers:

**Americas: +1 866 635 6805**
**Asia Pacific Region: +61 298 888322**
**Europe: +44 (0) 1628 540028**

- For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

Astellas may request additional information from the investigator to ensure the timely completion of accurate safety reports. Refer to the study procedures manual for specific details on how to report SAEs.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the patient's CRF.

### 7.7.3. FDA Reporting Requirements

Per 21 CFR 312.32, the sponsor-investigator is required to notify the FDA and all participating investigators of potential serious risks within 15 calendar days of determining the information meets FDA reporting requirements.

Unexpected fatal or life-threatening suspected adverse reactions must be reported to the FDA by the sponsor-investigator via phone or fax within 7 calendar days.

Current FDA regulations require that all SUSARs (see definition in Section 7.6) occurring on this trial, other findings that suggest a significant risk to humans exposed to the investigational drug (e.g. information from pooled analysis of multiple studies), and any clinically significant increase in the rate of an expected serious adverse reaction be reported as an IND Safety Report. Refer to Table A below for guidelines for reporting these events to the FDA.

In order to meet these requirements, the sponsor-investigator will review all reported serious adverse events as they occur and will conduct a literature search to seek new safety information and review and analyze all safety information from this clinical trial at least annually and more frequently as appropriate.

**Table A:** Reporting Requirements

| Report Type | Method of Report | Responsible | Timeline[1] |
|---|---|---|---|

| | | Party | Fatal/Life-Threatening Event | |
|---|---|---|---|---|
| | | | **Yes** | **No** |
| Individual Report | Form 3500A (MedWatch)[7] | RN/CRA | 4 calendar days[5] | 10 calendar days[5] |
| Other Findings that Suggest *Significant Risk*[2] | Narrative[3] | PI | 4 calendar day[6] | 10 calendar days[6] |
| Clinically Significant Increased Frequency of Suspected Adverse Reactions[4] | Narrative | PI | 4 calendar days[6] | 10 calendar days[6] |

1: Report Due to CCTO IND Coordinator according to the specified timeline regardless of whether or not all information regarding the event is available. If applicable, a follow-up report should be provided to the IND Coordinator once additional information on the event is available.
2: An IND Protocol Amendment is also required to describe any changes to the protocol, consent, or overall conduct of the study made as a result of this information. All revised documents should be made available to the CCTO IND Coordinator at the time of IRB submission.
3: Copy of relevant publication(s) should be included if applicable.
4: Details of individual cases should be included as appropriate
5: From date event was reported to the sponsor-investigator
6: After information is received by the investigator and determined to meet reporting criteria
7: The MedWatch form only needs to be completed for events that require FDA reporting. A copy of the completed form should be maintained in the subject research chart and master IND file in the CCTO.

All other events (e.g. protocol deviations or other safety concerns) not meeting the requirements for IND Safety Reporting (per 21 CFR 312.32) but which require reporting to the IRB as an Unanticipated Problem will be reported to the FDA as an informational amendment or with the annual report as appropriate.

### 7.8. Clinical Laboratory Abnormalities and Other Abnormal Assessments

Results from protocol-specified laboratory tests or unscheduled evaluations that are outside reference range, should not routinely be recorded as AEs unless the following occurs:

The patient experiences signs and/or symptoms that are associated with a laboratory abnormality or the abnormality results in medical intervention (eg, anemia requiring transfusion, hypoglycemia that is symptomatic and/or requiring intervention, hypokalemia requiring potassium supplementation, or any abnormality that results in study drug dose modification); Other abnormal assessments (eg, echocardiogram, radiographs, vital signs) must be recorded as AEs (or SAEs) if they meet the definition of an AE (or SAE) as described above in **Sections 7.**

The investigator should assess the most severe laboratory result and evaluate the relationship of this to protocol treatment and the clinical condition. All clinically significant abnormal laboratory test results should be followed until they return to normal or become stabilized.

### 7.9. Expected Adverse Events

The Erlotinib Investigator's Brochure contains a complete description of the safety information for erlotinib. An unexpected AE or ADR is any event for which the nature or severity is not consistent with the information contained in the erlotinib Investigator's Brochure.

Based on clinical results, dermatosis or rash, diarrhea, fatigue, nausea, vomiting, stomatitis, headache, cough, dyspnea, and infection were the most frequently observed undesirable effects in cancer patients following exposure to oral erlotinib. Hematological toxicity has not b een observed in patients receiving single-agent erlotinib treatment.

Diarrhea (sometimes severe) has occurred in patients receiving oral erlotinib and was mostly managed by loperamide; however, reduction in the dose of erlotinib was occasionally necessary with continuous daily dosing. There have been rare reports of renal failure and hypokalemia and some were secondary to severe dehydration due to diarrhea, nausea, vomiting, and/or anorexia. In more severe or persistent cases of diarrhea that may lead to dehydration or in patients with aggravating risk factors of renal impairment, study drug therapy should be interrupted and appropriate measures should be taken including rehydration.

There have been infrequent reports of serious ILD, including fatal events, in patients receiving erlotinib for treatment of NSCLC and other advanced solid tumors. In Study BR.21 in NSCLC patients, the incidence of ILD (0.8%) was the same in the placebo and erlotinib groups [12]. However, one cannot completely rule out a potential causal relationship between erlotinib exposure and the rare occurrence of ILD.

In the event of acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever, study drug should be interrupted pending diagnosticevaluation (see **Table 6-2**). If ILD is diagnosed, study drug should be discontinued and appropriate treatment instituted as necessary.

For further details regarding AEs considered to be possibly associated with study drug, refer to the 'Summary of Data and Guidance for the Investigator' section of the erlotinib Investigator's Brochure.

### 7.10. Pregnancy and Breast Feeding

Erlotinib should not be used during pregnancy or while breast feeding. Men and premenopausal women of child bearing potential will follow an approved, medically accepted birth control regimen or agree to abstain from heterosexual intercourse while taking study drug and for 30 days following the last dose of study drug.

Pregnancy and lactation are exclusion criteria. If a female patient becomes pregnant while receiving study drug or within 90 days after the last dose of study drug, the sponsor must be immediately notified of the pregnancy. The patient must be followed during the entire course of the pregnancy with perinatal and neonatal outcomes recorded, even if completely normal and without adverse events. At the time a site becomes aware of a pregnancy, a Pregnancy Report Form must be completed and submitted to the sponsor.

## 8. LABORATORY CORRELATES

**A tumor block or 10, 10-micron thick unstained slides must be available for study entry. These should be sent to:**

Rajani Kanteti, PhD
900 East 57th Street
KCBD Building 7240
Chicago, IL 60637
Telephone: 773-702-7875
Fax: 773-702-9268
Email: rkanteti@medicine.bsd.uchicago.edu

### 8.1. EGFR

#### 8.1.1. Extraction of DNA

- Three 10 um thick sections are cut from each paraffin embedded tissue block and placed into a microcentrifuge tube using clean forceps. Or 10, 10-micron unstained slides.

- The microtome blade, tweezers and other equipments that could come into contact with the sample are carefully sterilized before processing each tissue block with care taken to minimize cross contamination.

- The DNA extraction is carried out according to Sato et al. (2001) with minor modifications.

- The tissue sections are resuspended in 0.3 ml of digestion buffer ( 50mM Tris /Hcl, pH 8.5, 1 mM EDTA and 1% Tween 20 ).

- The tube is tightly capped with a pinhole at the center.

- High power microwave irradiation is carried out for 1 to 1.5 min with irradiation time split into 15 seconds segment to prevent over boiling.

- The tubes are centrifuged while they are warm at 12000 x g for 10 minutes and placed on ice.

- Using a sterile tooth pick, the solid paraffin wax ring that is formed above the buffer is removed.

- Proteinase K is added to each sample to get the final concentration of 0.5 mg /ml and the tubes are incubated at $55^0$ C in a water bath for 48 hrs with constant shaking.

- After two days of digestion with proteinase k, Chelex –100 (Biorad) is added to each sample to final concentration of 5% and the mixture is vortexed and heated at $95^0$ C for 10 minutes to inactivate the proteinase K.

- The samples are then centrifuged for 5 minutes at 12000 x g and the sup containing DNA is transferred to a new tube and stored at $-20^0$ or $4^0$ C.

- The amount of DNA extracted is quantitated by running an aliquot on 0.8% Agarose gel. PCR to determine □□globin transcripts is performed on all the DNA samples using BGLO3 and BGLO4 primers as described and the expected product is 355 bp (Coates et al, 1991).

- The above ensures the suitability of extracted DNA for amplification of specific genes.

### 8.1.2. PCR

- Exons 18 to 24 (inclusive) of *EGFR* are individually amplified by polymerase chain reaction (PCR).

- PCR conditions are:

    - one cycle of 95ºC for 5 minutes;
    - 30 cycles of 95ºC for 30 seconds, 57 ºC for 30 seconds, 72ºC for 1 minute;
    - and one cycle of 72ºC for 7 minutes.

- PCR products are treated with ExoSAP-IT (USB Corp., Cleveland, OH, USA) and sequenced by Big Dye Terminator Chemistry (Applied Biosystems, Weiterstadt, Germany).

- Chromatograms are analyzed for mutations using Mutation Surveyor v2.61 (Softgenetics).

## 8.2. Immununhistochemical analyses.

Immunohistochemistry for EGFR, p-EGFR, MET, vimentin, E-cadherin, CBL:

- IHC staining will be performed using biotin-free HRP-labeled polymer complex bound to secondary antibody (DAKO Cytomation, Carpinteria, CA).

- We will utilize the slides provided to us from the frozen tissues, and they should be 5 micron thick. We are requesting 10 slides per case.
- The primary antibody will be applied at room temperature for 1 hour. For c-Met expression, primary antibodies will include anti-c-Met (Zymed mouse monoclonal).
- For EGFR, the primary antibody will be the mouse monoclonal anti-human EGFR, clone 2-18C9 (Dako, Carpinteria, CA).
- For CBL, we will use the CAB004350 antibody (www.proteinatlas.org).
- The primary mouse will be the mouse monoclonal IgG2 antibody against E-cadherin (clone 36, BD Biosciences, Franklin Lakes, NJ).
- For vimentin, we will use the CAB000080 antibody (www.proteinatlas.org).
- Slides will then be developed for 5 min with 3-3'-diaminobenzidine (DAB) chromogen, counterstained with hematoxylin, and coverslipped.
- Negative controls will be performed by substituting the primary antibody step with non-immune mouse immunoglobulins.
- Results will be assessed qualitatively by light microscopy: Immunohistochemistry from tumor and adjacent normal tissue will be compared and grading will be for negative stain (0), weak stain (1+), moderate stain (2+), and strong expression (3+).

### 8.3. Serum biomarkers

#### 8.3.1. SMRP

- 1 mL of blood is removed by phlebotomy and placed in red top tube.
- Lab analysis performed by serology lab at the University of Chicago.

#### 8.3.2. CA 125

- 1 mL of blood is removed by phlebotomy and placed in red top tube.
- Lab analysis performed by chemistry lab at the University of Chicago.

## 9. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to administration of protocol therapy. Scans and x-rays must be done within 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

| | Pre-study, pre-screen[a] | Pre-study, post-screen[b] | Cy 1, D 1[c] | Cy 1, D 8[c] | Cy 1, D 15[c] | Cy 1, D 21[c] | Cy 2, D 1[c] | Cy 3, D 1[c] | D 1[c, d] | Off study[e] |
|---|---|---|---|---|---|---|---|---|---|---|
| Erlotinib[f] | | | X ---------- X | | | | | | | |
| Informed Consent (Screening) | X[a] | | | | | | | | | |
| Tissue analysis for EGFR | X | | | | | | | | | |
| Informed Consent (Treatment) | | X[b] | | | | | | | | |
| Demographics | | X | | | | | | | | |
| Medical History | X | X | | | | | | | | |
| Concurrent meds | | X | X ---------- X | | | | | | | |
| Physical exam | | X | X | | X | | X | X | X | |
| Vital signs | | X | X | | X | | X | X | X | |
| Height | | X | | | | | | | | |
| Weight | | X | X | | X | | X | X | X | |
| Performance status | | X | X | | X | | X | X | X | |
| CBC w/diff, plts | | X | X | | X | | X | X | X | |
| Serum chemistry, LFTs[g] | | X | X | | X | | X | X | X | |
| Adverse event evaluation | | | X ---------- X | | | | | | | |
| Tumor measurements | | X | Tumor measurements are repeated every 2 cycles. Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | |
| Radiologic evaluation | | X | Radiologic measurements should be performed every 2 cycles (CT or MRI chest, abdomen, and pelvis) | | | | | | | |
| B-HCG[h] | | X[h] | | | | | | | | |
| CA-125 and SMRP[i] | | | X[i] | | | | | X[i] | X[i] | |

a: Pre-study period prior to results of EGFR mutational analysis; patients are required to sign initial screening consent to have their tissue tested for EGFR mutations; treatment consent can not be signed until results have returned as positive for tumor exhibiting an EGFR mutation
b: Pre-study period after results of EGFR mutational analysis; if no mutation noted, unable to enroll in treatment study; if mutation noted, must sign treatment consent to receive erlotinib on trial
c. Office visits can be +/- 2 days from official date in cycle.
d: Day 1 of each subsequent cycle
e: Off study evaluation
f: Erlotinib 150 mg daily; see section 6.1 for dose modifications as appropriate
g: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
h: B-HCG: To be done ≤ 14 days before randomization for women of childbearing potential. Repeat while on study (through Post-treatment) only if clinically indicated.
i: Tumor markers (CA-125 and soluble mesothelin-related peptide (SMRP)) to be performed at baseline and then every 2 cycles at time of tumor radiologic evaluation.

## 10. MEASUREMENT OF EFFECT

### 10.1. Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee version 1.1[35].

#### 10.1.1. Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with erlotinib.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

#### 10.1.2. Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques (CT, MRI, x-ray) or as $\geq$10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not to be considered measurable.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

### 10.1.3. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US) When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

### 10.1.4. Response Criteria

**Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

**Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Incomplete Response/
Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be

confirmed at a later time by the review panel (or Principal Investigator).

**Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Response for this Category Also Requires: |
|---|---|---|---|---|
| CR | CR | No | CR | ≥4 wks. Confirmation |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks. Confirmation |
| PR | Non-PD | No | PR | |
| SD | Non-PD | No | SD | documented at least once ≥4 wks. From baseline |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD* | Yes or No | PD | |
| Any | Any | Yes | PD | |

36. In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

### 10.1.5. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

### 10.1.6. Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression.

## 11. REGULATORY AND REPORTING REQUIREMENTS

### 11.1. Adverse Events Reporting Guidelines

The descriptions and reporting system of adverse events is discussed in **Section 7.0.**

**Data Submission Guidelines**

For information regarding registration procedures, see **section 4.0.**

Study data should be submitted every four (4) weeks to fax # 773-834-1798. Study data includes dosing/infusion records, laboratory results, radiology reports, adverse event (AE) log, MD visit notes, and when applicable hospitalization records. All SAEs should be reported within 24 hours (see **Section 7.0** for details).

### 11.2. Data Safety and Monitoring

Data Safety and Monitoring will occur at the weekly University of Chicago Mesothelioma Conference meetings on Monday afternoons, which are lead by senior level medical oncologists. At each meeting, all active studies will be reviewed for safety and progress toward completion. Toxicities and adverse events will be reviewed at each meeting and a Data Safety and Monitoring form will be completed for each protocol and signed by either the principal investigator, the chairman of the section or by his designate if the chairman is not available. Auditing of 20% of patient charts will take place to ensure quality control and accuracy of documentation.

## 12. STATISTICAL CONSIDERATIONS

### 12.1. Study Design/Endpoints

Definition of primary outcome/endpoint:

1. Objective response rate according to RECIST 1.1 criteria[22]

Definition of secondary outcomes/endpoints:

1. PFS – time from study enrollment until disease progression or death

2. OS – time from study enrollment until death

3. Toxicity – per NCI CTCAE criteria version 4.0

4. Disease control rate – SD + PR + CR.

5. The percentage of patients who have activating EGFR mutations among all screened patients, to be reported along with a 95% confidence interval.

Analytic plan for primary objective:

The exact 95% confidence interval of the response rate will be reported.

Analytic plan for secondary objectives:

If the study proceeds to the second stage, progression-free and overall survival will be analyzed using the Kaplan-Meier method[36]. The log-rank test as well as the Cox PH model will be applied to examine the association between the response status and survival. The adjusted p-values and 95% confidence interval will be reported. Analysis will be by intent-to-treat with the exception that patients who withdraw prior to receiving any medication will be declared non-evaluable and replaced. Correlation of EGFR mutations with response, PFS, and OS will be exploratory in nature due to small sample size.

Exploratory analytic plan for laboratory objectives:

The aims of tumor tissue biomarker analyses include determining eligibility and exploring the prognostic and predictive effects of differing *EGFR* mutations and other biomarkers from tissue and serum on response rate, PFS, and/or OS. Cox regression models for PFS and OS will be used to evaluate the effect of specific *EGFR* mutations noted on efficacy outcomes. Exploratory analyses of other biomarkers and combinations of biomarkers will be conducted using appropriate statistical methods in a data-dependent way.

Sample size justification:

The sample estimation is completed using the Simon's optimal two-stage design method. A true 10% response rate would be uninteresting whereas a response rate of 30% would indicate that further study is warranted (i.e., p0=0.10 and p1=0.30 in the Simon terminology). Using an alpha level of 0.10 and 90% power, 12 patients will be enrolled in the first stage and if $< 1$ responses are observed the trial will be terminated. Otherwise, an additional 23 patients will be enrolled for a total of 35 patients, and if $< 5$ responses are observed the agent will not be considered sufficiently active to warrant further study. If 6 or more responses are observed the drug will be considered worthy of further study. This design provides a 65% probability of early stopping if, in fact, the true response rate is only 10%.

As MPeM is a rare disease, however, and the true rate of EGFR mutations is unknown, we will institute an 'early stopping rule' which requires an evaluation of the rate of EGFR mutations noted after 24 patients have been screened. Trial accrual is anticipated at 2 patients per month, 24 patients per year. If $\leq 2$ of those 24 patients are noted to have an EGFR mutation, the phase II trial will be discontinued and further screening for EGFR mutations will also cease. Observing 2 or fewer mutations in the first 24 patients is very unlikely (probability $< 0.01$) if the true rate is 31%; it is also unlikely even if the true rate is as low as 20% (probability = 0.11). A minimum 20% rate of EGFR mutations would be considered acceptable for the trial to proceed as the first stage of trial development requires 12 patients to be enrolled with EGFR mutations, requiring 2.5 years for completion at this rate.

However, despite this 'early stopping rule', any decision to terminate the trial will be undertaken in consultation with the sponsor, who may decide to continue enrollment if it appears that a positive signal of drug activity has been observed.

## 12.2. Sample Size/Accrual Rate

The University of Chicago is one of the leading institutions in the world for the treatment of mesothelioma. The most conservative estimate based on our current numbers would support a projection of at least 2 patients/per month for evaluation of EGFR status. Based on an expected mutation rate of 31%, 39 patients would need to be screened for 12 patients to be found with EGFR mutations for stage 1 of the trial and this would take 1.6 years.

## 12.3. Reporting and Exclusions

### 12.3.1. Evaluation of toxicity.

All patients will be evaluable for toxicity from the time of their first treatment with erlotinib..

### 12.3.2. Evaluation of response.

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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## APPENDIX A

### Performance Status Criteria

| **ECOG Performance Status Scale** | | **Karnofsky Performance Scale** | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

## Appendix B

## CYP3A4 and CYP1A2 Inhibitors/Inducers

| CYP3A4 Inhibitors | CYP3A4 Inducers |
|---|---|
| Delaviridine | Efavirenz |
| Indinavir | Nevirapine |
| Nelfinavir | |
| Ritonavir | Barbiturates |
| Saquinavir | Carbamazepine |
| | Glucocorticoids |
| Amiodarone | Modafinil |
| Aprepitant | Phenobarbital |
| Chloramphenicol | Phenytoin |
| Cimetidine | Rifampin |
| Ciprofloxacin | St. John's wort |
| Clarithromycin | Troglitazone |
| Diethyl-dithiocarbamate | Pioglitazone |
| Diltiazem | Rifabutin |
| Erythromycin | |
| Fluconazole | |
| Fluvoxamine | |
| Gestodene | |
| Itraconazole | |
| Ketoconazole | |
| Mibefradil | |
| Mifepristone | |
| Nefazodone | |
| Norfloxacin | |
| Norfluoxetine | |
| Verapamil | |
| | |
| Grapefruit juice | |

| CYP1A2 Inhibitors | CYP1A2 Inducers |
|---|---|
| Amiodarone | Insulin |
| Cimetidine | Methyl-cholanthrene |
| Fluoroquinolones | Modafinil |
| Fluvoxamine | Nafcillin |
| Furafylline | Beta-naphthoflavone |
| Methoxsalen | Omeprazole |
| Mibefradil | Tobacco |

Refer to the following website for a complete list: http://medicine.iupui.edu/flockhart/table.htm

## Appendix C
## PATIENT'S MEDICATION DIARY

**Today's date** _____ **Agent:** _____
**Patient Name**_____(*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. **Erlotinib** should be stored at room temperature.
3. You will take erlotinib daily.
4. **Erlotinib** should be TAKEN WITH WATER ONLY IN THE MORNING, 1 HOUR BEFORE OR 2 HOURS AFTER MEALS.

   Total morning dose: ___ mg **erlotinib**; Dosing: __ 150 mg tablets, __ 100 mg tablets, and __ 25 mg tablets.
3. Record the date, the number of tablets of each size of tablet that you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form and your bottles of study drug tablets when you return for each appointment.
6. Please record missed or skipped doses. Do not share your study drug supply, and wash your hands after touching

| | | | **Erlotinib** | | **Comments** |
|---|---|---|---|---|---|
| **Day** | **Date** | **Time of dose** | **Number of tablets** | **Total Dose** | |
| 1 | | | | | |
| 2 | | | | | |
| 3 | | | | | |
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**Patient's signature**_____

**Physician's Office will complete this section:**

1. Date patient started protocol treatment

   _____
2. Date patient was removed from study

3. Patient's planned total daily dose

4. Total number of tablets taken this month

5. Physician/Nurse/Data Manager's Signature